REMARKS/ARGUMENTS

I. STATUS OF THE CLAIMS

Claims 14 – 28 and 41 – 53 are pending and under examination.

Claim 14 is amended herein to more particularly point out and distinctly claim that which Applicants regard as the invention. In particular, claim 14 was amended to recite "an open extraction channel, wherein the inner surface of the open extraction channel is comprised of a solid phase extraction surface". Support for the amendment can be found in Applicants' specification for example, on page 8, lines 6 – 10, page 19, lines 26 – 27 and page 29, lines 19 - 20.

The amendment is fully supported by the application as filed and does not introduce new matter. Entry of this amendment is respectfully requested.

II. INTERVIEW SUMMARY

Applicants thank the Examiner for the very informative personal interview conducted April 23, 2009. Present were inventor Doug Gjerde, Applicants' representative, Sue Kalman, Examiner Keri Moss and Supervisor Vickie Kim. During the interview, Applicants presented an animated PowerPoint presentation depicting the methods of the invention and shared exhibits of the open extraction channels used with the invention. Applicants explained that the claimed methods are performed in open channels rather than packed columns and agreed to amend the claims to recite "open channels". The difference between protein complexes and complex mixtures of proteins was also discussed.

III. EXAMINER'S RESPONSE TO AMENDMENT

Applicants appreciate the withdrawal of the requirement for election of claims 43 – 48.

Applicants additionally thank the Examiner for withdrawal of the objection to claims 19, 22, 43 and 44 and for the withdrawal of the rejection of claims 19, 22, 43 and 44.

IV. CLAIM AMENDMENTS

All references cited in the § 102 and § 103 rejections teach methods performed in packed columns comprised of chromatography media (e.g., beads) held in place with frits or filters.

In contrast, the methods of the instant invention are not performed in packed columns comprised of chromatography beads or frits. To clearly distinguish the claimed methods from those performed with chromatography beads or in packed columns, Applicants amended independent claim 14 herein to recite "an **open** extraction channel, wherein the **inner surface of the open channel is comprised of a solid phase extraction surface**."

The following passages from Applicants specification describe the open extraction channels of the claimed invention[1].

> The subject invention pertains to solid phase extraction channels, and methods of using the same for extracting an analyte from solution. In some embodiments these **extraction channels are open**, that is, they are **not packed with resin or other forms of chromatographic beads** used in conventional chromatography. Rather, the channel is open and the extraction phase consists of an extraction surface bound either directly or non-directly to the channel surface. The extraction process involves flowing solvent, such as sample solvent, desorption solvent, and optionally a wash solvent, through the open channel, or some portion of the channel. In some preferred embodiments, the open channel is a capillary, i.e., an extraction capillary. [Emphasis added]
>
> In preferred embodiments, the extraction surface covers the entire ***inner periphery*** of the extraction channel, as opposed to on just one face of the channel.[2] [Emphasis added]
>
> Fig. 1 shows a tubular channel 2, the ***inner surface of which is coated with a solid phase extraction medium*** 4.[3] [Emphasis added]

Because the claimed extraction channels are **open** and because they are **not packed with resin or other forms of chromatographic beads**, the methods of the invention cannot be

[1] Applicant's specification, page 8, lines 5 – 13.
[2] Applicant's specification, page 8, lines 14 – 15.
[3] Applicant's specification, page 19, lines 26 – 27.

anticipated by or obvious over methods performed in packed columns packed with chromatographic beads.

If the Examiner believes these amendments do not adequately distinguish the claimed methods from those performed on packed columns, Applicants invite the Examiner to telephone the undersigned so we can work together to identify alternative claim language. Since the Examiner personally saw the devices of the claimed invention last April, Applicants believe it should be relatively straightforward to agree on the claimed invention.

V. RESPONSE TO EXAMINER'S RESPONSE

The claimed invention relates to methods for purifying multi-protein complexes. During prosecution, a significant issue has arisen over the meaning of the term, "multi-protein complex". In the last response (dated December 19, 2008), Applicants argued that the cited references failed to teach extraction of multi-protein complexes. In the instant rejection, the Examiner disagreed with Applicants' argument[4]. The Examiner states that the cited references teach mixtures of proteins from blood or plasma and that cellular proteins inherently interact, even when outside of the cell. The Examiner reasons that due to this inherent interaction, the proteins isolated in the cited references are actually part of multi-protein complexes when they attach to a solid phase.

According to the MPEP[5], the words of a claim must be given their "plain meaning" and that "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." Applicants submit that the Examiner is not giving the term, "multi-protein complex" its plain meaning. The term, multi-protein complex refers to a group of associated proteins that **perform a particular biological function.** Examples of common biological functions accomplished by protein complexes include DNA replication, transcription and translation. To further demonstrate this fact, Applicants submit herewith (as Appendix A) a list of commonly-studied multi-protein complexes.

The Examiner believes that the proteins isolated by Agnew, Gobom and Strosberg are actually components in a multi-protein complex because they are isolated from mixtures or lysates that undergo inherent interaction. Contrary to the Examiner's assertion, proteins do not

[4] Office action, paragraph 17.
[5] MPEP 2111.01

interact randomly or haphazardly. This is illustrated by the following quote from one of the most widely-used textbooks, Biochemistry, by Voet & Voet. "Proteins, because of their multiple polar and nonpolar groups, stick to almost anything; **anything, that is, but other proteins**. This is because the forces of evolution have arranged the surface groups of proteins so as to prevent their association under physiological conditions. If this were not the case, their resulting nonspecific aggregation would render proteins functionally useless. [6]" (bold emphasis added)

The Examiner may be correct in assuming that blood or plasma samples contain multi-protein complexes, even when outside the cell. However, it is not true that these protein complexes would necessarily be isolated using the methods of Agnew, Gobom or Strosberg. On the contrary, Agnew, Gobom and Strosberg all teach isolation of individual proteins, not protein complexes.

On page 8 of the Office action, the Examiner states that the term "open channel" was not recited in the claims. In response, the claims were amended herein to include the term, "open channel".

With respect to the term, "extraction channel", the Examiner states that Applicants have not cited portions of the instant specification that define the term. To remedy this, Applicants cited three sections of the specification (above in section IV) describing the open extraction channels of the claimed invention.

The Examiner states that it is her duty to give the claims their broadest reasonable interpretation and provides the definition of the term "channel" from Webster's II New Riverside Dictionary as "a means of passing, transmitting and communication." First, this is an extremely broad definition taken from a non-technical dictionary. According to the MPEP, claims must be given their broadest reasonable interpretation **consistent with the specification**[7]. [emphasis added].

Second, in the Office action, the Examiner states, "Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims." The Examiner cites *In re Van Geuns*, 988, F.2d 1181,26 USPQ2d 1057 (Fed. Cir. 1993). Interestingly, the Examiner makes reference to this case at least 3 times[8]. It is puzzling that the Examiner provides this broad definition of a channel while repeatedly stating that claims must be

[6] Page 180, Biochemistry, 2nd Ed., Voet and Voet. 1995, Wiley & Sons.
[7] MPEP, 2111.
[8] Office action, paragraphs 18, 20 and 21.

interpreted in light of the specification.

Third, the Examiner's definition of the term, "channel" does not take into account that the claims were directed to an "extraction channel". No one skilled in the art considers a packed column to be an extraction channel.

Actually, the term channel can be used at times when talking about a packed bed column. In this context, a channel is an undesirable passageway through the medium or adjacent to the medium. When a packed bed develops channels, it can no longer separate mixtures of components because the liquid flow is no longer going through the bed in a uniform manner. A packed bed column that has a channel or "is channeling" is useless and ready to be thrown out. The bed is said to be fractured.

VI. REJECTIONS UNDER 35 U.S.C. § 102

A. AGNEW

The Examiner rejected claims 14 and 17–18 under 35 U.S.C. § 102(e) as being anticipated by Agnew *et al.* (U.S. Patent Application Publication No. 2004/0171034, "Agnew"). The Examiner states that Agnew teaches a method for extracting a multi-protein complex comprising the steps of introducing a sample solution comprising the multi-protein complex into an extraction channel which has an inner surface comprising an extraction surface that binds the multi-protein complex, passing a wash solution through the channel and passing a first desorption solution through the channel, thereby eluding the first protein (citing paragraph ([0014]). Applicants respectfully traverse the rejection.

Agnew teaches method for isolation of phosphorylated molecules. In the paragraph cited by the Examiner, Agnew discusses current methods used for enrichment of phophopeptides from complex mixtures. These methods include column chromatography with an immobilized metal affinity medium[9].

In this response, Applicants amended independent claim 14 to recite "an open channel, wherein the inner surface of the open channel is comprised of a solid phase extraction surface". For a reference to be deemed anticipatory, it must teach every element of the claims. Agnew fails to do this because Agnew fails to teach

- methods performed in an **open** extraction channel wherein the **inner surface**

[9] Agnew, paragraph [0014].

of the channel is comprised of a solid phase extraction surface

- methods whereby a multi-protein complex is adsorbed to the extraction surface

Agnew does not teach an open channel. Agnew teaches conventional column chromatography. Agnew does not teach an inner surface comprised of a solid phase extraction phase. Instead, Agnew teaches a solid support comprised of chromatography beads. Furthermore, Agnew does not teach adsorption of a multi-protein complex to a column (see arguments above in section IV).

Therefore, independent claim 14 is not anticipated by Agnew. Since claims 17 and 18 depend from claim 14, and thus further limit claim 14, claims 17 and 18 are not anticipated by Agnew.

Claims 17 recites a list of multi-protein complexes and claim 18 is drawn to method of claim 14 wherein the second protein remains adsorbed to the extraction surface. Claims 17 and 18 are not anticipated by Agnew because Agnew does note teach an open extraction channel wherein the inner surface of the channel is comprised of a solid phase extraction surface and Agnew does not teach methods for extracting a multi-protein complex.

In view of the foregoing, the withdrawal of the rejections under 35 U.S.C. § 102(e) is respectfully requested.

B. Zimmerman

Claims 14, 17–20, 22–24, 26–28, 41–42 and 49–53 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zimmerman *et al.* (U.S. Patent 4,361,509, "Zimmerman"). In response, Applicants respectfully traverse these rejections.

Zimmerman teaches methods for purification of the procoagulant, factor VIII. using chromatography beads as a solid support. In the section of Zimmerman cited by the Examiner, Zimmerman performs immunoadsorption of factor VIII with a monoclonal antibody adsorbent bound to a suitable substrate such as agarose beads[10]. After the purification, Zimmerman concentrates the factor VIII using an affinity chromatography column containing

[10] Zimmerman, column 2, lines 53 – 57.

aminhexyl substituted agarose[11]. Zimmerman additionally states that other solid substrates can be used for the immunoadsorption step[12] and that the method can be performed in a batch format instead of a column[13].

First, as Applicants argued above (in section B), claim 14 was amended herein to recite an **open** extraction channel. Zimmerman does not teach an open channel. Zimmerman teaches traditional column chromatography using chromatography beads.

Second, Zimmerman does not teach an **inner surface of the open extraction channel comprised of a solid phase extraction surface**. Zimmerman only teaches the use of beads, a conventional solid support.

Therefore, independent claim 14 is not anticipated by Zimmerman. Since claims 17–20, 22–24, 26–28, 41–42 and 49–53 all depend from claim 14, and thus further limit claim 14, claims 17–20, 22–24, 26–28, 41–42 and 49–53 cannot be anticipated by Zimmerman.

Claims 41 and 42 are drawn to extraction methods wherein the wash solution or desorption solutions are flowed back and forth through the extraction channel. These methods are discussed throughout Applicants specification including the following passage[14].

> It is possible to repeatedly expose the sample, wash and desorption solvent to the extraction surface (e.g., by simply moving it back and forth through the channel). In the case of sample, this can mean greater extraction efficiencies and hence greater recoveries. In the case of desorption solvent, this can translate into dramatically reduced desorption volume, resulting in a more enriched desorbed sample. Concentrations of the sample can be increased by using only a small slug of desorbing solvent that passes back and forth over the stationary phase before it is deposited from the channel to the target.

The Examiner alleges that Zimmerman teaches a desorption solution that flows back and forth through the column due to fluid dynamics[15], however this is not the case. Conventional chromatography techniques utilize unidirectional flow in order to minimize band broadening and product dilution. Hence bidirectional flow is specifically avoided in the practices

[11] Zimmerman, column 3, lines 2 – 8.
[12] Zimmerman, column 6, lines 23 – 30.
[13] Zimmerman, column 7, lines 54 – 62.
[14] Applicants' specification, page 4, lines 12 – 18.
[15] Office action, paragraph 9, page 4.

described by Zimmerman. Therefore, claims 41 and 42 are not anticipated by Zimmerman for this additional reason.

Claim 49 recites a 3-dimensional extraction surface. The term 3-dimensional relates to placement of extraction agents in 3 dimensions by derivatizing the channel with a polymer. A 3-dimension extraction surface has denser placement of extraction agents and thus, higher capacity than the corresponding 2-dimensional extraction surface or monolayer. The 3-dimensional binding phase allows for packing of analyte molecules in a 3rd dimension. Zimmerman does not teach a 3-dimensional extraction surface inside a capillary channel. Therefore, claim 49 is not anticipated by Zimmerman for this additional reason.

Lastly, claim 52 recites performing the method in a plurality of channels operated in parallel and claim 53 is drawn to carrying out the method in a solid block having one of more passageways running therethrough. The Examiner states that Zimmerman performs the method in a plurality of channels operated in parallel or in a solid block having one or more passageways running through and cites columns 7 and 8. Applicants could find no such methods in columns 7 and 8.

In view of the foregoing, the withdrawal of the rejections under 35 U.S.C. § 102(e) is respectfully requested.

VII. REJECTIONS UNDER 35 U.S.C. § 103(a)

A. ZIMMERMAN OR AGNEW IN VIEW OF GOBOM

Claims 15 – 16 and 43 – 48 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman or Agnew, supra, in view of Gobom *et al.* ("Sample Purification and Prepartion technique Based on nano-scale Reversed-phase Columns for the Sensitive Analysis of Complex Peptide Mixtures by Matrix-assisted laser Desorption/ionization Mass Spectrometry", *J. Mass Spectrom.*, vol. 34 pages 105–116 (1999), hereinafter "Gobom"). Applicants traverse the rejection.

The Examiner states that neither Zimmerman nor Agnew expressly teach purging the extraction channel with a gas prior to passing a desorption solution through the channel wherein the extraction surface remains substantially solvated after the purging step. Gobom teaches the use of conventional reversed phase packed medium in the preparation of peptides for analysis using MALDI/TOF-MS[16]. The Examiner states, "It would have been obvious to modify

[16] Gobom, page 107.

Zimmerman or Agnew with the capillary column of Gobom in order to gain the advantages of decreasing costs, increasing speed of reaction and making the reaction more efficieint."

Applicants respectfully disagree. Claim 14 was amended herein to recite **open extraction channels** wherein the **inner surface is comprised of a solid phase extraction surface**. As Applicants argued above, neither Zimmerman nor Agnew discloses the use of **open extraction channels** wherein the **inner surface is comprised of a solid phase extraction surface**, as required in the amended claims. Gobom does not supply the missing teachings. Gobom teaches a fused silica capillary filled with chromatography medium[17]. Gobom does not teach an open channel. Gobom does not teach an **inner surface is comprised of a solid phase extraction surface.** Applicants argue it would not be obvious to one of ordinary skill in the art to develop **open channel** extraction methods based on the combined teachings of Agnew, Zimmerman and Gobom. Therefore claim 14 is not obvious over the combination of Agnew, Zimmerman and Gobom. Since claims 15 – 16 and 43 – 48 depend from claim 14, they are not obvious over the combination of Agnew, Zimmerman and Gobom.

Claims 15 and 16 recite methods for purging the extraction channel with a gas prior to the desorption step. Claim 15 is drawn to methods wherein the extraction channel is substantially free of bulk liquid and claim 16 recites an extraction surface that remains substantially solvated after the purging step. The Examiner states that Gobom also teaches a method wherein the channel is purged before adding the desorption solution and that it would have been obvious to modify Zimmerman or Agnew by purging the channel with gas before adding the desorption solution in order to gain the predictable results of a smooth and continuous liquid flow during the purification of the protein."

Again, Applicants disagree. Gobom states, "The column was run **completely dry** by pressing air through it for a few seconds.[18]" Neither claim 15 nor claim 16 teach running the column completely dry. In claim 16, the extraction surface remains substantially solvated. With respect to claim 15, the following text from Applicants' specification describes that even when extraction channel is substantially free of bulk liquid, the analyte and/or extraction surface **can be fully hydrated**[19].

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[17] *Ibid.*
[18] *Ibid.*
[19] Applicants' specification, page 3, lines 19 – 22.

> In another embodiment, the invention provides an extraction channel containing a bound analyte, where the extraction channel is substantially free of bulk liquid, e.g., as the result of a purge step. While substantially free of bulk solution, the analyte and/or extraction surface **can be fully hydrated**. [emphasis added]

Thus, if the analyte can be fully hydrated, the column cannot be considered completely dry as taught by Gobom. Therefore, claims 15 and 16 are not obvious over the combination of Agnew, Zimmerman and Gobom for this additional reason.

In view of the foregoing, the withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

B. ZIMMERMAN

Claim 21 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman, *supra*. Claim 21 is drawn to a method of extracting a multi-protein complex comprised of at least three proteins. The multi-protein complex is bound to the open channel and the component proteins are eluted stepwise by varying the desorption solution.

The Examiner alleges claim 21 is obvious over the teachings of Zimmerman and states, "It would have been obvious for one of ordinary skill in the art to modify Zimmerman by using a third desorption solution to elute a third protein in order to obtain the predictable results of separating the third protein from the multi-protein complex.[20]"

As Applicants argued above, claim 14 was amended herein to recite an **open extraction channel** and Zimmerman does not teach open extraction channels. Claim 14 was also amended to recite an inner surface of the open extraction channel comprised of a solid phase extraction surface. Zimmerman does not teach an inner surface comprised of a solid phase extraction surface. Zimmerman teaches traditional chromatography in a column in which the solid phase is comprised of beads. Zimmerman's extraction surface is actually located on the chromatography beads. It would not be obvious to one of ordinary skill in the art to perform open channel solid phase extraction based on the traditional chromatography methods taught by Zimmerman. In view of the foregoing, the withdrawal of the rejection under 35 U.S.C. § 103(a)

[20] Office action, page 5, paragraph 12.

is respectfully requested.

C. ZIMMERMAN IN VIEW OF AGNEW

Claim 25 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Zimmerman, *supra*, in view of Agnew, *supra*. Claim 25 is drawn to particular agents used during stepwise elution method. After the multi-protein complex is bound to the open channel, it can be interrogated by eluting the component proteins stepwise using a variety of desorption solutions. This process is detailed in Applicants' specification[21].

The Examiner states, "...it would have been obvious to modify Zimmerman with the reactive groups of Agnew et al. in order to gain the advantages of having a resulting phosphate-binding compound that is useful for conjugation to phosphorylated target molecules." Applicants traverse the rejection.

First, as Applicants argued above, neither Zimmerman nor Agnew teach open channels and it would not be obvious to perform the claimed extraction methods in open channels based on the teachings in traditional packed columns.

Second, the Examiner proposes that Applicants would be motivated to combine the teachings of Zimmerman and Agnew to gain the advantages of having a phosphate-binding compound that is useful for conjugation to phosphorylated target molecules. In order to establish a *prima facie* case of obviousness when the references do not teach or suggest all the claim limitations, Office personnel must explain why the differences between the cited art and claimed invention would have been obvious to one of ordinary skill in the art[22]. Applicants submit the Examiner has not provided a reasonable explanation of why it would have been obvious to one of ordinary skill in the art to modify Zimmerman with the reactive groups of Agnew. Based on the claimed invention and Applicants' specification, it is evident that having a phosphate-binding compound useful for conjugation to phosphorylated target molecules is not related to the claimed invention.

In view of the foregoing, the withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

D. ZIMMERMAN IN VIEW OF STROSBERG

Claims 26–27 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over

[21] Applicants' specification, page 57, line 8 through page 58, line 9.
[22] MPEP, section 2141.

Zimmerman, *supra*, in view of Strosberg *et al.* (EP 1 178 318 A1, hereinafter "Strosberg"). Claim 26 recites the method of independent claim 14 wherein the multi-protein complex is comprised of a recombinant bait protein and claim 27 is drawn to the method of claim 26 wherein the bait protein comprises a fusion tag. The Examiner states, "…it would have been obvious for one of ordinary skill in the art to use a recombinant bait protein with a fusion tag in order to bind to a specific polypeptide of interest and to gain the additional advantages and predictable result of optically determining when that polypeptide has been bound to the recombinant bait protein." Applicants traverse the rejection.

First, as Applicants argued above, neither Zimmerman nor Strosberg teach extraction in **open channels**. Strosberg teaches a novel class of compounds used to detect a polypeptide of interest[23]. The section of Strosberg cited by the Examiner refers to immunoaffinity chromatography performed on a column[24]. Furthermore, it would not be obvious to perform the claimed methods of extraction in open channels based on the teachings of chromatography in traditional packed columns.

Second, the Examiner proposes that Applicants would be motivated to combine the teachings of Zimmerman and Strosberg to gain the additional advantages and predictable result of optically determining when that polypeptide has been bound to the recombinant bait protein. In order to establish a *prima facie* case of obviousness when the references do not teach or suggest all the claim limitations, Office personnel must explain why the differences between the cited art and claimed invention would have been obvious to one of ordinary skill in the art[25]. Applicants submit the Examiner has not provided a reasonable explanation of why it would have been obvious to one of ordinary skill combine Zimmerman with Strosberg because the claimed invention does not involve optical determination.

In view of the foregoing, the withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

[23] Strosberg, column 5, lines 9 – 14.
[24] Strosberg, column 38, line 55 through column 39, line 3, column 39, lines 41 - 45.
[25] MPEP, section 2141.

CONCLUSION

Entry of this Amendment is respectfully requested. An early and favorable action on the merits is earnestly solicited.

The Commissioner is hereby authorized to charge $405 for an RCE and $65 for a one-month extension of time to Deposit Account No. 50-2852. In the event that an extension of time is required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely. The Commissioner is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-2852.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (408) 267-7214.

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Attachments:

Appndix A. Protein complex List